SFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Aberg et al.

Application No.: 09/447,218 Art Unit: 1623

Filed: November 23, 1999 Examiner: Lawrence E. Crane

For: METHODS FOR TREATING URTICARIA USING DESCARBOETHOXYLORATADINE

Attorney Docket No.: 4821-362 (JD 208423-999361)

RESPONSE TO EXAMINER'S INTERVIEW SUMMARY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the Examiner-Initiated Interview Summary ("the Summary") dated December 19, 2005, which appears to have been issued in response to a voice-mail message left to the Examiner by Mr. Anthony Insogna, an attorney for Applicants.[1]

In the Summary,[2] the Examiner indicates that his statement that Applicants' representative made "disparaging remarks" regarding the newly submitted declaration is factually correct. Applicants strongly disagree with this notion since Applicants' representative never made "disparaging remarks" as the Examiner appears to believe. For the record, Applicants point out that their representative simply invited the Examiner to review and comment upon the Tarantino Declaration during the interview.[3] Therefore,

---

[1] The Interview Summary was not mailed to Applicants, but it appears on the electronic record, *i.e.*, PAIR. Applicants request either withdrawal from the record or official mailing of this paper.

[2] Applicants note that the first and second interview summaries discussed herein were issued in connection with application no. 09/039,260 rather than the current application. However, since the majority of interview time was spent on the discussion of the current application, Applicants submitted their response to the first interview summary, and are submitting this response, in the present case. To complete the record in this application, copies of the first and second interview summaries are attached hereto as **Exhibits A and B**.

[3] Specifically, Applicants' representative asked whether the Examiner would be able to briefly review Tarantino Declaration and provide his opinion regarding the declaration. To paraphrase, Applicants' representative asked if the Examiner could provide his opinion as to whether the declaration is sufficient or insufficient to address the issues raised by the Examiner on the meaning of tumor promotion data provided in Example 4 of the current specification, and if insufficient, how the Examiner would recommend improving it. The Examiner appears to have

Applicants point out that the Examiner's belief or statement that such "disparaging remarks" were made by Applicants' representative is simply incorrect.

Further, it is stated in the Summary that Applicants' representative "did not like repetition of his description of a portion of examiner's analysis of the Storm[s] declaration in an Office action as an example of examiner sarcasm." Applicants do not dispute that Applicants' representative stated that he was under an impression that certain portion of the Examiner's analysis regarding Storms Declaration may have been sarcasm. However, Applicants respectfully point out that such a statement is simply irrelevant to the patentability of the pending claims, and thus, has no place in "substance of the interview."

It is also stated in the Summary that Applicants' representative "did not like ... [the] overemphasis on the Storm[s] declaration." By his statement, Applicants' representative was referring to the fact that a disproportionate portion of the first interview summary was devoted to the Examiner's own version of the discussion of Storms Declaration, while little description of additional evidence presented by Applicants (*e.g.*, prior art that teaches away from the claims, scientific articles supporting patentability of the claims, and legal precedent contradicting the Examiner's positions) was provided despite the fact that a significant amount of time was spent on the discussion of such evidence.

In addition, it is stated in the Summary that Applicants' representative expressed his concern regarding the failure to discuss "newly submitted documents first made available to examiners during the interview and not yet made of record." Applicants strongly disagree because the references discussed during the interview (*e.g.*, Michel, Parslew, McClintock, Yap, and Goodman & Gilman's) were all submitted previously with Applicants' responses and Appeal Brief, and thus, are properly in the record of the current application. For example: Michel, Parslew, Goodman & Gilman's, and McClintock were submitted as Exhibits G, H, I, and J, respectively to Applicants' Appeal Brief filed on November 8, 2001; and Yap was submitted as Exhibit E to Applicants' response filed April 23, 2001. Thus, the Examiner's allegation that the references discussed during the interview were "first made available" to himself is factually incorrect. Indeed, the Examiner's statement goes to prove Applicants' point that the Examiner has failed to consider all of the relevant evidence in the record.[4]

---

focused only on the latter portion of this statement after the interview and turned that into "disparaging remarks."

[4] Despite this admission that the references have not in fact been considered, the Examiner maintains in the Office Action that all relevant evidence in the record has been considered, which causes a great concern to Applicants with regard to the Examiner's ability or willingness to properly examine this application through allowance.

Finally, Applicants would like to take this opportunity to submit a copy of Ring *et al.*, *Allergy*, 56: 28-32 (2001) ("Ring"), attached hereto as **Exhibit C**. Although Ring was published after the priority date of this application, Ring shows that, contrary to what the Examiner alleges, there was no reasonable expectation of successfully using any and all antihistamine even in 2001, much less at the time of this invention, in the treatment of urticaria. (*See* Ring, **Exhibit C**, Abstract ("The goal of treatment is rapid, long-lasting symptom relief, and currently available antihistamines fail to provide this in many cases.")).

Furthermore, Ring discloses, after the priority date of this application, that DCL provides much improved safety and efficacy for the treatment of urticaria than other available antihistamines. (*Id.*, Conclusion). This disclosure is precisely in accord with the claims of the current application -- the method of using DCL is safe and effective in treating urticaria despite motivation or suggestion to the contrary. Therefore, Applicants respectfully submit that Ring provides an additional evidence to what is already in the record that shows the pending claims are patentable.

Conclusion

No fee is believed to be due for the submission of this paper and the Exhibits. If any fees are required, however, please charge such fees to Jones Day Deposit Account No. 503013. A copy of this sheet is enclosed.

Respectfully Submitted,

Date: January 19, 2006

L0209

Hoon Choi (Limited Recog. No.)
Jones Day
51 Louisiana Avenue, N.W.
Washington, DC 20001-2113
(202) 879-3939

For: Anthony M. Insogna (Reg. No. 35,203)
Jones Day
12750 High Bluff Drive, Suite 300
San Diego, CA 92130
(858) 314-1200

Enclosure

DCJD: 505306.1

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	09/039,260	ABERG ET AL.	
	Examiner	Art Unit	
	L. E. Crane	1623	

All Participants:

(1) *L. E. Crane*.

(2) *Anthony M. Insogna (response to voice mail)*.

Status of Application: *after final rejection*

(3) _____.

(4) _____.

Date of Interview: *19 December 2005*

Time: _____

Type of Interview:

☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☒ No
If Yes, provide a brief description:

Part I.

Rejection(s) discussed:
None

Claims discussed:
None

Prior art documents discussed:
None

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
See Continuation Sheet

Part III.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

(Examiner/SPE Signature)

(Applicant/Applicant's Representative Signature – if appropriate)

Continuation of Substance of Interview including description of the general nature of what was discussed:

Applicant's representative objected to some portions of the interview summary of the interview conducted on 12/13/2005.

Applicant's representative's objections were as follows:
i) he did not like the notation of his own disparaging remarks regarding the newly submitted declaration and failure to repeat or explain said remarks,
ii) he did not like repetition of his description of a portion of examiner's analysis of the Storm declaration in an Office action as an example of examiner sarcasm,
iii) he did not like what applicant's representative characterized as an overemphasis on the Storm declaration, and
iv) he did not like the failure to discuss newly submitted documents first made available to examiner's during the interview and not yet made of record.

Examiner responds that the record appeared to be accurate and that applicant had not made any criticism which suggested that a factual error has been made.

Documents made of record must be reviewed by the assigned examiner during the normal course of examination, and this will happen when the documents in question are made of record by applicant.

Applicant's representative is reminded that he is free to submit his own recapitulation of the interview as a separate filing or as part of the next response to the Office action of record.

Examiner also replied (by voice mail) that the interview had already been sent for scanning and that the SPE who read, reviewed, and approved the interview summary prior to a copy being FAXed to Mr. Choi was James O. Wilson and that all complaints not made directly to instant examiner should be forwarded to Mr. Wilson who may be reached at the telephone number provided in previous recent Office actions.

Examiner-Initiated Interview Summary

Application No.	Applicant(s)
09/039,260	ABERG ET AL.
Examiner	**Art Unit**
L. E. Crane	1623

All Participants:

(1) *L. E. Crane*.

(2) *Anthony M. Insogna*.

Status of Application: *related to 09/447,218 & 10/989,514: all cases discussed.*

(3) *S. Anna Jiang SPE*.

(4) *Hoon Choi & Robert Barker (Assignee Rep.)*.

Date of Interview: *13 December 2005* **Time:** *2PM*

Type of Interview:
- ☐ Telephonic
- ☐ Video Conference
- ☒ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☒ No
If Yes, provide a brief description:

Part I.

Rejection(s) discussed:
All of record in all three cases

Claims discussed:
All of record in all three cases, independent claims in particular

Prior art documents discussed:
Vilani '716 patent and Berkow (Merck Manual)

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
See Continuation Sheet

Part III.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

(Examiner/SPE Signature) (Applicant/Applicant's Representative Signature – if appropriate)

Continuation of Substance of Interview including description of the general nature of what was discussed:

Applicant's indicated that there had been a decision at the PTO BPAI wherein Mr. Insogna had successfully argued that inherency did not apply in the case wherein the metabolite of a known pharmaceutical was being claimed; i.e. the metabolite is separately patentable. Applicants also indicated that they intended to file an additional declaration in the instant cases, a complementary copy of which was supplied during the interview. Examiner's appreciate this gesture but the document is not yet officially of record so cannot be considered until it has been filed and made of record in the E-dan database of scanned documents for the instant case or cases. Applicant's representative made what appeared to be disparaging remarks directed to the newly submitted complementary declaration and when queried concerning what he had said, applicant's representative declined the opportunity to either repeat or explain his comments. And at the end of the interview applicant's indicated that the 10/989,514 case would probably be permitted to go abandoned and that the possibility of filing RCE's for the remaining cases was a possibility. When requested to comment on this possibility, examiner's indicated that any RCE's filed would be accepted but that no RCE's would be solicited from this or any other applicant by instant examiners. In a clarification applicant's noted that loratadine was the active ingredient in the pharmaceutical product sold as Claratin™ while the products sold as Clarinex™ contain the active ingredient descarbethoxyloratadine (DCL) which is the active ingredient in the instant claimed method of treatment and pharmaceutical composition claims at issue in this interview.

During the balance of the interview applicant's representative argued strenuously that the Storm declaration provided an adequate basis for a finding of allowability. Examiner's counter argued with the view that applicant's were misusing the opportunities afforded to introduce evidence to support arguments in obviousness rejections to alter inappropriately the policy of the PTO in re evidentiary requirements in medical claims. Alternatively examiner's noted that Storm's criticisms of the Villani reference amounted to an attempt to remove Villani from consideration as a reference in the instant case by casting doubt on its validity, a strategy which cannot be permitted except in the event that applicant's file a separate action requesting re-examination of Villani. In a discussion of the Storm declaration and examiner's comments on the declaration applicant's representative suggested that examiner's comments in re Storm in an Office action were prefaced by what applicant's suggested was merely sarcasm. Examiner's objected to this interpretation strenuously indicating that the complement to Dr. Storm as a knowledgeable person was intended as a complement, but that examiner's stood by their view that Storm was applying the wrong standard, and that applicant's were encouraged to submit declarations wherein the PTO standard provides the basis for arguments, as opposed to the FDA standard ("safe and effective") which Storm repeated referred to throughout his declaration.

In a discussion of the pharmaceutical composition claims in 09/039,260 and 10/989,514, applicant's asserted that their claims were patentably distinguishable over the Villani disclosure. Examiner's respectfully and strenuously disagreed, noting in particular column 11 at lines 29-33 of Villani (4,659,716) wherein the dosage regimen of " ... from 5 to 100 mg/day ..." included the further limitation permitting the dosage to be administered " ... in two to four divided doses to achieve relief of the symptoms," a reading which applicant's representative was unable to agreed permitted dosages to be as low as 1.25 mg/dosage. Examiner's insisted that this reading was valid and that this reading meant that the overlap between applicant's claimed range of dosage substantially overlaps with that disclosed by Villani in either solid dosage forms or transdermal dosage forms. No agreement or compromise on claim language was achieved during this discussion and examiner's seriously doubt that any compromise is possible.

In a discussion of the method of treating claims in 09/447,218, applicant's argued strenuously that the 103 rejection based on the combination of Villani and Berkow (Merck Manual) was insufficient and cited the references discussed in the Storm declaration (Michele and Parslew in particular) as providing serious doubt concerning whether one of ordinary skill would have been motivated to combine the two references as a basis for finding the instant claims obvious in light of the cited prior art. Applicant's argued that at the time of filing of the Villani application there was discussion in the pharmaceutical arts concerning possible side effects of DCL based on side effects of other antihistamines, a argument that examiner's found unconvincing because applicant's appeared to be making extrapolations equivalent to findings of guilt by association; i.e. no facts appeared to have directly implicated DCL as having disqualifying side effects and that in any case such arguments represent another example of Storm's mistaken application of the FDA "safe and effective" standard. Examiner's suggested that applicant's reliance on such arguments implied that applicant's were soliciting a rejection alleging inoperativeness under 35 U.S. Cl. §101, a suggestion which applicant's rejected out of hand as incorrect. Examiner's respectfully disagreed with these attacks

on the Office action and noted that Villani clearly disclosed and claimed pharmaceutical compositions DCL as an "antihistamine" with "anti-allergic" effects, that Berkow taught that antihistamines were useful in the treatment of urticaria (hives), and that Berkow's teaching that provides the ordinary practitioner with sufficient guidance to conduct routine experimentation in the search for an antihistamine appropriate to treat hives including a choice (DCL) taught and claimed by Villani. Examiner's also argued that the choice of the practitioner conducting routine experimentation is not constrained by a PTO utility standard or a PTO medical testing policy analogous to the FDA's "safe and effective" standard. and that applicant's reliance on the arguments of Storm appeared to be a flaw in their strategy because of Storm's excessive reliance on FDA standards. No agreement or compromise on claim language was reached during the extensive discussion of this issue.

NOTE: A copy of this interview summary in a different format but with the same text aside from this note was FAXed to applicant's representative Mr. Hoon Choi on December 16, 2005.

Examiner-Initiated Interview Summary

Application No.	Applicant(s)
09/039,260	ABERG ET AL.
Examiner	**Art Unit**
L. E. Crane	1623

All Participants:

(1) *L. E. Crane*.

(2) *Anthony M. Insogna (response to voice mail)*.

Status of Application: *after final rejection*

(3) _____.

(4) _____.

Date of Interview: *19 December 2005*

Time: _____

Type of Interview:

☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☒ No
If Yes, provide a brief description:

Part I.

Rejection(s) discussed:
None

Claims discussed:
None

Prior art documents discussed:
None

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
See Continuation Sheet

Part III.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

(Examiner/SPE Signature)

(Applicant/Applicant's Representative Signature – if appropriate)

Continuation of Substance of Interview including description of the general nature of what was discussed:

Applicant's representative objected to some portions of the interview summary of the interview conducted on 12/13/2005.

Applicant's representative's objections were as follows:
i) he did not like the notation of his own disparaging remarks regarding the newly submitted declaration and failure to repeat or explain said remarks,
ii) he did not like repetition of his description of a portion of examiner's analysis of the Storm declaration in an Office action as an example of examiner sarcasm,
iii) he did not like what applicant's representative characterized as an overemphasis on the Storm declaration, and
iv) he did not like the failure to discuss newly submitted documents first made available to examiner's during the interview and not yet made of record.

Examiner responds that the record appeared to be accurate and that applicant had not made any criticism which suggested that a factual error has been made.

Documents made of record must be reviewed by the assigned examiner during the normal course of examination, and this will happen when the documents in question are made of record by applicant.

Applicant's representative is reminded that he is free to submit his own recapitulation of the interview as a separate filing or as part of the next response to the Office action of record.

Examiner also replied (by voice mail) that the interview had already been sent for scanning and that the SPE who read, reviewed, and approved the interview summary prior to a copy being FAXed to Mr. Choi was James O. Wilson and that all complaints not made directly to instant examiner should be forwarded to Mr. Wilson who may be reached at the telephone number provided in previous recent Office actions.

Allergy 2001: 56: 28–32
Printed in UK. All rights reserved

ALLERGY
ISSN 0108-1675

Desloratadine in the treatment of chronic idiopathic urticaria

Chronic idiopathic urticaria (CIU) is a common dermatologic disorder that may severely impair quality of life. Patients may suffer symptoms such as pruritus and disfigurement due to wheals for years or decades. Advances have been made in the last 10 years with the identification of an autoimmune pathogenesis in a significant proportion of patients. Despite this, treatment remains symptomatic, and antihistamines are the first choice of therapy once the diagnosis of CIU has been established. The goal of treatment is rapid, long-lasting symptom relief, and currently available antihistamines fail to provide this in many cases. Desloratadine is a novel, potent H_1-receptor antagonist with additional inhibitory effects on inflammatory mediators such as cytokines and adhesion molecules. Newly published data on the efficacy and safety of desloratadine in CIU is highly encouraging, suggesting that the drug may improve symptom control above that currently available.

J. Ring, R. Hein, A. Gauger
Division of Environmental Dermatology and Allergy
GSF TUM, Dermatologische Klinik, Techniche
Universität München, Munich, Germany

Key words: allergic cascade; chronic idiopathic urticaria; desloratadine.

Professor Johannes Ring
Dermatologische Klinik
Techniche Universität München
Biedersteinerstrasse
D-29802 München
Germany

Chronic idiopathic urticaria (CIU) is a common skin condition that affects 0.1–3% of people in the USA and Europe (1) and accounts for nearly 75% of all chronic urticaria cases (2). CIU is defined classically as the appearance of hives/wheals on most days for more than 6 weeks, in the absence of a causative physical or environmental trigger (3). Therefore, the diagnosis of CIU is mainly one of exclusion, and the clinical investigative process can be lengthy. Hematologic, biochemical, immunologic, and endocrine assays are needed to provide direct or indirect evidence of systemic allergic, inflammatory, infectious, or autoimmune processes that may cause chronic urticaria. Thereafter, sensitivity to foods, environmental agents/pollutants, and the presence of chronic infection or occult malignancy must all be excluded before a diagnosis of CIU can be finally established (4).

The duration of CIU varies greatly from patient to patient, with some individuals suffering irritating symptoms such as pruritus for decades. Patients with CIU have measurable decrements in quality of life, primarily due to recurrent itch, poor sleep, and the physically unappealing nature of the lesions. The activities of daily life and social life are badly affected by CIU. Indeed, the magnitude of this impairment of quality of life approximates that of chronic heart disease (5). Therefore, the goal of treatment in CIU is rapid and prolonged symptom control, thus allowing a return to normal sleep patterns and social activity.

Antihistamines have long been the mainstay of treatment for patients with CIU (6), and second-generation drugs have replaced older agents to a large extent for reasons of safety. However, the therapeutic response is not uniform across all patients, and improvements are continually sought with respect to pharmacologic potency and duration of action. Desloratadine (AERIUS®, Schering-Plough Corp.) is a new nonsedating H_1-receptor antagonist with the strongest peripheral H_1-blocking effects yet reported. Desloratadine also has a range of inhibitory effects on mediators and cytokines that play an important role in chronic allergic inflammation. These antiallergic and anti-inflammatory activities may translate into improved clinical responses in patients with CIU. This brief review assesses newly available clinical data on desloratadine in CIU and places it in the context of our current immunopathologic understanding of CIU.

Pathophysiology of CIU

The wheals of chronic urticaria have a characteristic appearance, namely, a pinkish-red center that merges into a red surround. These wheals are itchy and edematous and may coalesce to form giant wheals that are very uncomfortable and unsightly. In many cases, angioedema with infiltration and swelling at the lower dermal and submucosal levels accompanies chronic urticaria. Macroscopically, the wheals of CIU bear a striking resemblance to the cutaneous late-phase response (LPR) to allergen (7). Because of this similarity, many patients endure exhaustive investigations for causative dietary or household allergens. These physical similarities to the cutaneous LPR are also reflected at the microscopic level. Histologically, increased numbers of mast cells, T helper cells, and neutrophils can be identified. Cellular activation also occurs, with the release of large amounts of histamine

and other mediators e.g. tryptase, chymase, heparin, leukotrienes, prostaglandins, and platelet-aggregating factor in affected skin (8). Upregulation of adhesion molecules and cytokines can also be observed (9, 10). The result is perivascular leukocyte infiltration and tissue edema, although these structural changes are not associated with structural damage to the dermis. Indeed, apart from damage inflicted by scratching, CIU wheals resolve completely and spontaneously within a day or so.

Given the micro- and macroscopic similarities between CIU wheals and the cutaneous LPR to allergen, a great deal of research has focused on establishing the nature of the link. An important breakthrough was made in the early 1990s. It had been noted previously that autologous intradermal injection of serum from patients with CIU could cause wheals, pointing to a circulating factor that could activate cutaneous mast cells. Moreover, autoimmune thyroid disease was found to occur at a higher frequency in patients with CIU. Greaves' group in London identified an IgG autoantibody in the serum of patients with CIU that was specifically directed against the α-subunit of the high-affinity IgE receptor, FcεRI (11). This autoantibody was functional, in that it caused mast-cell activation and histamine release. These anti-FcεRI antibodies or distinct functional anti-IgE autoantibodies (12) can be identified in up to 45% of CIU patients. This implies that CIU may be predominantly an illness in which symptoms are produced by autoimmune targeting of the body's allergen defense system. Basophils, which also express FcεRI, are affected in CIU, and basophil numbers and immunologic reactivity are decreased in CIU (13), possibly via autoimmune mechanisms.

Despite this important advance, the pathogenesis of CIU remains uncertain in a significant proportion of cases. However, it is likely that mast cells may be activated by various inherited or conditioned immune and nonimmune events. Autoantibodies to other factors may degranulate mast cells via separate cell-surface receptors. The susceptibility of mast cells to degranulation by unknown serum factors and the magnitude of this response may be determined by genetically polymorphic molecular events.

Pharmacologic profile of desloratadine

Desloratadine is the active metabolite of loratadine, which itself has been widely used in CIU. Pharmacologically, desloratadine has a number of advantages over its parent compound, primarily in terms of novel anti-inflammatory activity and enhanced H_1-receptor blockade. Desloratadine binds avidly to human histamine H_1-receptors *in vitro;* indeed, it has the highest H_1-receptor affinity of all currently available antihistamines (15). The K_i for desloratadine was 0.87 nM, compared with 175 nM for fexofenadine and 138 nM for loratadine. This translates into relative potencies of 201, 3.7, 1.2, and 1.0 for desloratadine, cetirizine, loratadine, and fexofenadine, respectively (16). This receptor binding is selective, as desloratadine has a low affinity for both the H_2 and the muscarinic receptors (15, 17). Furthermore, desloratadine does not penetrate the blood–brain barrier in animal studies, a fact which has been confirmed by the lack of sedation or cognitive impairment in clinical trials (18 20).

Apart from its H_1-receptor inhibition, desloratadine also has novel antiallergic activity. *In vitro* experiments have demonstrated that desloratadine inhibits the release by mast cells and basophils not only of histamine (21), but also tryptase and the arachidonic acid products leukotriene C_4 and prostaglandin D_2 (22). These mediators are generated by mast cells in response to activation (by allergen and other agents), and are important in promoting local inflammation and cellular infiltration. It is now widely recognized that local mast-cell activation leads to widespread upregulation of inflammatory cytokines, chemokines, and adhesion molecules. The net result of this cascade of activity is the maturation, chemoattraction, accumulation, and activation of chronic allergic cells such as basophils and eosinophils, leading to late-phase local inflammation. Desloratadine has been shown to inhibit many of these important mediators, including the cytokines IL-4, IL-13, IL-6, TNF-α, and GM-CSF (23–25), the chemokines IL-8 and RANTES (26), and adhesion molecules such as P-selectin and ICAM-1 (27, 28). Furthermore, desloratadine reduces eosinophil chemotaxis and activation *in vitro* (29), although the effects on other chronic inflammatory cells and in the *in vivo* situation are less certain. However, it does appear that desloratadine has biologic activities that may translate into greater clinical efficacy in diseases such as CIU.

Clinical experience with desloratadine in CIU

A double-blind, placebo-controlled multicenter trial of desloratadine in moderate-to-severe CIU has recently been completed. This large study ($n=190$) revealed important information on the efficacy, tolerability, and onset of action of desloratadine in patients with CIU. Patients with active CIU received 5 mg desloratadine or placebo daily for a maximum period of 6 weeks. The patients attended daily for the first 4 days and then weekly for 6 weeks or until discontinuation. Symptoms such as pruritus, the number of hives, and the size of the largest hive were scored twice daily, while interference with sleep was scored in the morning and interference with daily activities was scored only in the evening (all scored as 0 [none] to 3 [severe]). Composite scores of current and reflective (over the previous 12 h) symp-

toms were also assessed morning and evening, thus providing four scores per day. The primary efficacy parameter was the mean change from baseline in reflective pruritus score during the first 7 days of treatment. In the desloratadine group, pruritus scores fell by 56.0%, compared with 21.5% with placebo ($P<0.001$). Similar decreases with desloratadine were seen in secondary efficacy parameters such as number of hives (−48.4% *vs.* −15.8%; $P<0.001$), size of the largest hive (−49.7% *v.* −17.0%; $P<0.001$), and total symptom score (−51.6% *vs.* −19.3%; $P<0.001$). Desloratadine treatment also significantly improved sleep and activities of daily life in comparison with placebo. Over week 1 of treatment, interference with sleep fell by 53.0% and 18.4% ($P<0.001$) with desloratadine and placebo, respectively. Interference with daily activity mirrored this with falls of 50.2% and 20.0% ($P<0.001$) in patients receiving desloratadine and placebo, respectively.

When considered in isolation, these results over week 1 demonstrate admirable clinical efficacy with desloratadine in patients with active moderate-to-severe CIU. Further analyses over the entire length of the trial demonstrate the durability of desloratadine's clinical effects. With respect to pruritus, patients in the desloratadine group maintained a statistically significant improvement over placebo ($P<0.001$) to the end of the trial at week 6 (Fig. 1). Similarly, all other secondary efficacy parameters, including interference with sleep and daily activities, were significantly better in the desloratadine group than in the placebo group (Fig. 2a and b).

One of the primary aims of treatment in CIU is fast symptom relief. Close examination of the data from this trial revealed that desloratadine had a rapid onset of action. Assessments of all symptoms were made daily for the first 4 days of the study. After a single dose of medication, pruritus had fallen by 44.6% in the desloratadine group, compared with only 19.5% in those taking placebo ($P<0.001$). This rapid onset of action and prolonged duration of efficacy were mirrored in total symptom score, interference with sleep/daily activities, and hive size/number (Fig. 3).

Desloratadine was rated highly by both patients and investigators with respect to overall CIU improvement and therapeutic response during the trial. These joint investigator/subject assessments demonstrated the significant superiority of desloratadine over placebo at all

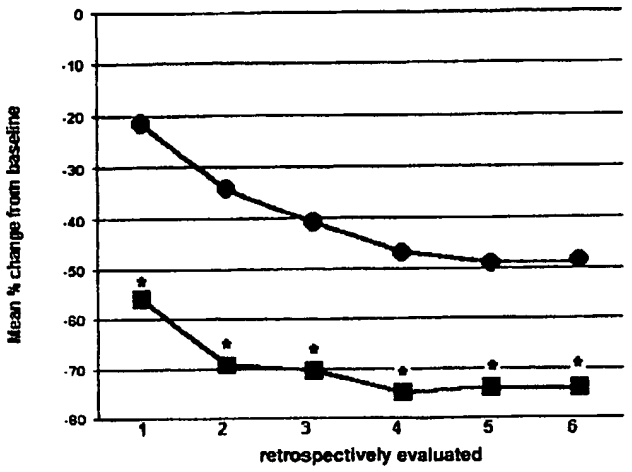

Figure 1. Subject-evaluated mean 12-h retrospectively evaluated pruritus score (primary efficacy parameter). Patients received either desloratadine 5 mg (n=95) or placebo (n=94) once daily. Symptom scores were rated from 0 (absent) to 3 (very severe). Desloratadine (squares), placebo (circles).
*$P<0.001$ *vs* placebo.

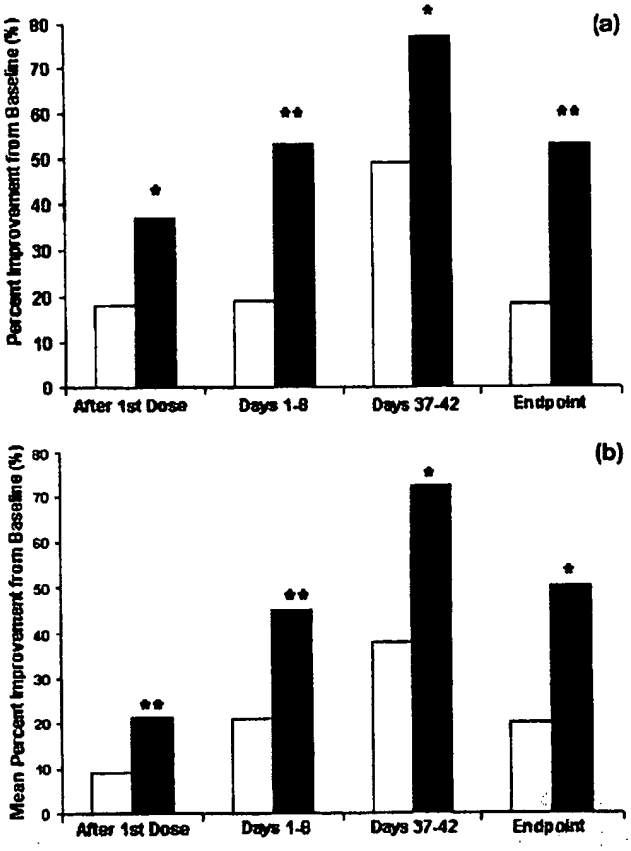

Figure 2a. Results of subject-evaluated AM prior 12-h interference with sleep analysis. Patients received either desloratadine 5 mg (filled column) or placebo (open column) once daily, and rated interference with sleep in morning before taking study medication. From first dose onward (i.e., rated day 2, AM), desloratadine provided significantly greater improvements in sleep scores than placebo. *$P<0.001$ *vs* placebo; **$P<0.05$ *vs* placebo.
Figure 2b. Results of subject-evaluated PM prior 12-h interference with daily activity results. Patients received either desloratadine 5 mg (filled column) or placebo (open column) once daily (AM) and rated interference with daily activities in evening. From first dose onward (i.e., rated day 1, PM), desloratadine provided significantly greater improvements in daily activity scores than placebo. *$P<0.001$ *vs* placebo; **$P=0.02$ *vs* placebo.

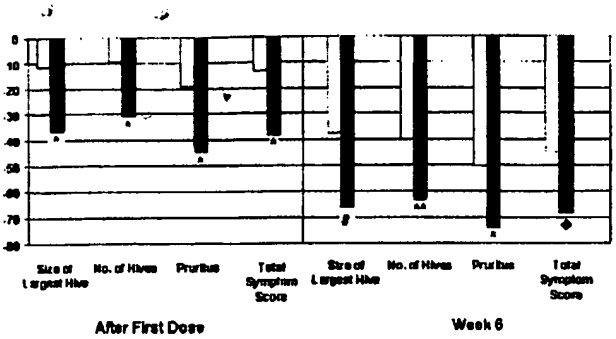

Figure 3. Rapid onset of action and prolonged duration of efficacy of desloratadine 5 mg in CIU. Results of hive number/size, pruritus score, and total symptom score are shown after first dose and at week 6 of trial. Desloratadine demonstrated significant effects on efficacy parameters from first dose, and effects lasted for full duration of trial. $*P<0.001$; $\#P=0.04$, $**P=0.02$; $\blacklozenge P=0.002$.

time points (days 4, 8, 15, 29, and 43) with respect to CIU condition ($P<0.001$) and therapeutic response ($P\leq 0.002$).

Desloratadine was safe and well tolerated during the trial. The most common adverse events in both groups were headache, viral infection, fatigue, and pharyngitis. Only one severe adverse event was considered to be related to desloratadine (headache in one patient); however, this subject continued in the trial. ECG, laboratory, and vital sign data were all similar in the desloratadine and placebo groups, and no clinically relevant changes were noted.

Conclusion

Our understanding of the pathophysiology of CIU has deepened over the past decade, with the identification of functional autoantibodies in a significant proportion of patients. However, the pathogenesis of CIU in more than 50% of cases remains unclear. As CIU can decrease quality of life significantly, the aim of treatment is to provide rapid and durable symptomatic relief. Despite the wide availability of nonsedating antihistamines, many patients continue to experience troublesome symptoms, sometimes for decades. This need may be met by desloratadine, a potent, nonsedating H_1-receptor antagonist with novel antiallergic and anti-inflammatory actions. Clinical experience in CIU has so far shown desloratadine to be a safe and effective treatment, providing rapid onset of action and long duration of symptom relief.

References

1. Sabroe RA, Greaves MW. The pathogenesis of chronic idiopathic urticaria. Arch Dermatol 1997;133:1003–1008.
2. Champion RH. Urticaria: then and now. Br J Dermatol 1988;119:427–436.
3. Greaves MW. Chronic urticaria. N Engl J Med 1995;332:1767–1772.
4. Ring J, Brockow K, Ollert M, Engst R. Antihistamines in urticaria. Clin Exp Allergy 1999;29 Suppl 1:31–37.
5. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol 1997;136:197–201.
6. Ring J, Behrendt H. H_1 and H_2 antagonists in allergic and pseudoallergic diseases. Clin Exp Allergy 1990;20 (Suppl):43–49.
7. Grattan CEH, Boon AP, Eady RAJ, Winkelmann RK. The pathology of the autologous serum skin test response in chronic urticaria resembles IgE-mediated late-phase reactions. Int Arch Allergy Appl Immunol 1990;93:198–204.
8. Kaplan AP, Horakova Z, Katz SI. Assessment of tissue fluid histamine levels in patients with urticaria. J Allergy Clin Immunol 1978;61:350–354.
9. Hermes B, Prochiazka A-K, Haas N, Jurgovsky K, Sticherling M, Henz BM. Upregulation of tumor necrosis factor α and interleukin-3 expression in lesional and uninvolved skin in different types of urticaria. J Allergy Clin Immunol 1999;103:307–314.
10. Möller A, Henz BM, Grutzkau A, et al. Comparative cytokine gene expression: regulation and release by human mast cells. Immunology 1998;93:289–295.
11. Hide M, Francis DM, Grattan CEH, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993;328:1599–1604.
12. Grattan CEH, Francis DM, Hide M, Greaves MW. Detection of circulating histamine releasing autoantibodies with functional properties of an anti-IgE in chronic urticaria. Clin Exp Allergy 1991;21:695–704.
13. Greaves M. Chronic urticaria. J Allergy Clin Immunol 2000;105:664–672.
14. Toubi-Blant A, Kessel A, Golan TD. Low dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. Allergy 1997;52:312–316.
15. Kreutner W, Hey JA, Anthes J, Barnett A, Young S, Tozzi S. Preclinical pharmacology of desloratadine, a selective and nonsedating histamine H_1-receptor antagonist. 1st communication: receptor selectivity, antihistaminic activity, and antiallergic effects. Arzneimittelforschung 2000;50:345–352.
16. Anthes JC, Richard C, West RE, et al. Functional characterization of desloratadine and other antihistamines in human H_1-receptors. Allergy 2000;55 Suppl 63:S279 (Abstract 994).
17. Kreutner W, Hey JA, Anthes J, Barnett A, Tozzi S. Preclinical studies of desloratadine, a non-sedating, selective histamine H_1-receptor antagonist with antiallergic activity. Allergy 2000;55 Suppl 63:S278 (Abstract 997).
18. Hey JA, Barnett A, Iorio L, Chiu P, Kreutner W. Desloratadine: cardiovascular, central nervous system, renal and gastrointestinal safety profile of this nonsedating H_1 antihistamine. Allergy 2000;55 Suppl 63:S278 (Abstract 996).
19. Rikken G, Schaaf MB, Danzig MR, Staudiger H. Desloratadine and alcohol co-administration: no increase in impairment of performance over that induced by alcohol alone. Allergy 2000;55 Suppl 63:S277 (Abstract 993).

20. Vuurman EFPM, Ramaekers JG, Rikken G, de Halleux F. Desloratadine does not impair actual driving performance: a 3-way crossover comparison with diphenhydramine and placebo. Allergy 2000;55 Suppl 63 (Abstract 945).
21. Kleine-Tebbe J, Josties C, Frank G, et al. Inhibition of IgE and non-IgE-mediated histamine release from human basophil leukocytes *in vitro* by a histamine H_1-antagonist, desethoxycarbonyl-loratadine. J Allergy Clin Immunol 1994;93:494–500.
22. Genovese A, Patella V, De Crescenzo G, De Paulis A, Spadaro G, Marone G. Loratadine and desethoxylcarbonyl-loratadine inhibit the immunological release of mediators from human Fc epsilon RI+ cells. Clin Exp Allergy 1997;27:559–567.
23. Schroeder JT, Schleimer RP, Lichtenstein LM, Kreutner W. Inhibition of cytokine generation and mediator release by human basophils treated with desloratadine. Clin Exp Allergy 2001 (in press).
24. Lippert U, Moller A, Welker P, Artuc M, Henz BM. Inhibition of cytokine secretion from human leukemic mast cells and basophils by H_1- and H_2-receptor antagonists. Exp Dermatol 2000;9:118–124.
25. Lippert U, Krüger-Krasagakes S, Moller A, Kiessling U, Czarnetzki BM. Pharmacological modulation of IL-6 and IL-8 secretion by the H_1-antagonist decarboethoxy-loratadine and dexamethasone by human mast and basophilic cell lines. Exp Dermatol 1995;4:272 276.
26. Lebel B, Bousquet J, Czarlewski W, Campbell AM. Loratadine reduces RANTES release by an epithelial cell line. J Allergy Clin Immunol 1997;99 S444 (Abstract 1802).
27. Molet S, Gosset P, Lasalle P, Czarlewski W, Tonnel AB. Inhibitory activity of loratadine and descarboxyethoxyloratadine on histamine-induced activation of endothelial cells. Clin Exp Allergy 1997;27:1167–1174.
28. Vignola AM, Crampette L, Mondain M, et al. Inhibitory activity of loratadine and descarboethoxyloratadine on expression of ICAM-1 and HLA-DR by nasal epithelial cells. Allergy 1995;50:200–203.
29. Agrawal DK, Berro A, Townley RG. Desloratadine attenuation of eosinophil chemotaxis, adhesion, and superoxide generation. Allergy 2000;55 Suppl 63:S276 (Abstract 990).